

*REMARKS/ARGUMENTS**The Pending Claims*

Claims 1, 4, 6-9, and 21-39 are currently pending. Claims 24-39 have been withdrawn in reply to a restriction requirement as being directed to a non-elected invention.

*The Amendments to the Claims*

Claim 1 has been amended to incorporate the subject matter of claims 2 and 5, and to correct matters of form. Claims 4 and 6-9 have been amended to correct matters of form. Claims 2, 3, and 5 have been cancelled, and claims 21 and 22 have been amended to change their dependency in view of these claim cancellations. No new matter has been added by way of these amendments.

*The Office Action*

Claim 3 is objected to under 37 C.F.R. § 1.75(c) as allegedly being an improper dependent claim. Claims 1-4 and 8-9 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by U.S. Patent 5,110,722 (Brockbank et al.). Claims 1, 3-9, and 21-22 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent 4,512,977 (Lundy) in view of Lavin et al., *British Medical Journal*, 292: 1448-1450 (1986). Claim 23 is rejected under 35 U.S.C. § 103(a) as allegedly obvious over Lundy in view of Lavin et al., in further view of WO 03/047604 (Kuklinski et al.). Reconsideration of the objection and rejections is respectfully requested.

*Discussion of Claim Objection*

Claim 3 is objected to under 37 C.F.R. § 1.75(c) because it allegedly does not further limit the subject matter of claim 1. Claim 3 has been cancelled, thereby mooted the objection.

*Discussion of Anticipation Rejection*

Claims 1-4 and 8-9 have been rejected under Section 102(b) as allegedly anticipated by Brockbank et al. This rejection is traversed for the reasons set forth below.

Claim 1, as amended, is directed to a pharmaceutical composition which comprises, in aqueous solution, (a) 5-500 µg/ml of a selenium-containing active substance, (b) 0.5-50 mg/ml of a corticoid-containing active substance, and (c) insulin.

Brockbank et al. discloses a method of cultivating cells, tissues, and organs using a solution that comprises selenium, insulin, and hydrocortisone. Brockbank et al., however, does not disclose a composition containing selenium and a corticoid in the range of concentrations currently claimed. In this respect, Brockbank et al. discloses a composition comprising transferrin, insulin, 2.5 ng/ml-7.5 ng/ml selenium, and 25 ng/ml-40 ng/ml hydrocortisone. These amounts of selenium and hydrocortisone are significantly less than the amounts of selenium and a corticoid required by the pending claims (i.e., 5-500 µg/ml of selenium and 0.5-50 mg/ml of a corticoid).

In view of the foregoing, Brockbank et al. does not disclose the subject matter of claim 1, or claims 4, 6-9, and 21-23 depending therefrom. Therefore, Applicants request that the anticipation rejection be withdrawn.

#### *Discussion of Obviousness Rejection*

Claims 1, 3-9, and 21-22 have been rejected under Section 103(a) as allegedly obvious over Lundy in view of Lavin et al. Claim 23 has been rejected under Section 103(a) as allegedly obvious over Lundy in view of Lavin et al. and Kuklinski et al. These rejections are traversed for the reasons set forth below.

For subject matter defined by a claim to be considered obvious, the Office must demonstrate that the differences between the claimed subject matter and the prior art “are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” 35 U.S.C. § 103(a); see also *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). The ultimate determination of whether an invention is or is not obvious is based on certain factual inquiries including: (1) the scope and content of the prior art, (2) the level of ordinary skill in the prior art, (3) the differences between the claimed invention and the prior art, and (4) objective evidence of nonobviousness. *Graham*, 383 U.S. at 17-18, 148 U.S.P.Q. at 467.

Consideration of the aforementioned Graham factors here indicates that the present invention, as defined by the currently pending claims, is unobvious in view of the cited references.

Regarding the scope and content of the prior art, Lundy discloses compositions comprising 0.05 mg-2.0 mg selenium by weight (preferably 0.5 mg-1.0 mg) for administration to humans to ameliorate the affects of certain physical injuries (e.g., lacerations and burns). Lavin et al. describes case reports of patients who received topical ocular steroids (e.g., hydrocortisone) as treatment for various ophthalmic conditions. Kuklinski et al. discloses pharmaceutical compositions containing selenite for the treatment of inflammatory diseases.

For purposes of the analysis here, and for the sake of argument, the level of ordinary skill in the art can be considered to be relatively high, such that a person of ordinary skill in the art would have an advanced degree and/or several years of experience in the relevant field.

Claim 1, as amended, is directed to a pharmaceutical composition which comprises, in aqueous solution, (a) 5-500  $\mu\text{g/ml}$  of a selenium-containing active substance, (b) 0.5-50 mg/ml of a corticoid-containing active substance, and (c) insulin. Neither Lundy or nor Lavin et al. discloses or suggests a pharmaceutical composition comprising selenium, a corticoid, and insulin, much less such a composition containing selenium and a corticoid in the concentrations presently claimed. Kuklinski et al. does not compensate for the deficiencies of the combination of Lundy and Lavin et al. In this respect, while Kuklinski discloses compositions containing a selenium-containing active substance (i.e., selenite), Kuklinski does not disclose or suggest a composition comprising selenium, a corticoid, and insulin.

If one of ordinary skill in the art were to prepare a pharmaceutical composition in accordance with the combined disclosures of Lundy, Lavin et al., and Kuklinski et al., the resulting pharmaceutical composition would not include 5-500  $\mu\text{g/ml}$  selenium, 0.5-50 mg/ml of a corticoid, and insulin because Lundy, Lavin et al. and Kuklinski et al. do not disclose or even suggest such a pharmaceutical composition. Moreover, the Office has provided no

reason why one of ordinary skill in the art would prepare such a pharmaceutical composition based on the disclosures of Lundy, Lavin et al., and Kuklinski et al.

Furthermore, the present invention involves surprising and unexpected results. Indeed, Applicants have demonstrated that the claimed composition surprisingly can be used to improve the treatment of sepsis, SIRS, or septic shock. Specifically, the specification describes a clinical study (see specification at page 9, last paragraph) in which the administration of selenium (i.e., sodium selenite as 1000 microgram bolus per day followed by further daily bolus injections with 1000 pg selenite for 14 days and 35 mg sodium selenate per day as a basis) together with hydrocortisone (i.e, 200 mg continuously over 24 hours for the complete duration of the severe infection) was shown to improve treatment of these diseases in patients for whom blood sugar was adjusted with insulin to be below 200 mg%. The mortality rate of patients treated only with selenium or hydrocortisone was reduced by approximately 10%-20%, whereas the mortality rate of patients treated with the combination therapy of the present invention (i.e., selenium, hydrocortisone, and insulin) was reduced by approximately 80%. Therefore, the combination of selenium, corticoid, and insulin exhibits a synergistic effect which surprisingly reduced the mortality rate in patients suffering from sepsis.

Considering all of the *Graham* factors together, the present invention would not have been obvious to one of ordinary skill in the art in view of the combination of cited references, particularly because the combination of cited references does not disclose or suggest the claimed invention, and because the present invention involves surprising and unexpected results. Accordingly, Applicants request that the obviousness rejection be withdrawn.

### *Conclusion*

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned agent.

Respectfully submitted,

A handwritten signature in dark ink, appearing to read "Melissa E. Kolom", is written over a horizontal line.

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